UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,266	12/08/2000	Richard Kuo	STAN-209	3109

24353 7590 09/06/2002

BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
AFREMOVA, VERA	
ART UNIT	PAPER NUMBER
1651	19

DATE MAILED: 09/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/733,266	Kuo et al.
Examiner	**Art Unit**
Vera Afremova	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 6, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-5, 13, and 15* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-5, 13, and 15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1, 3-5, 13 and 15 as amended [Paper No. 13 filed 2/03/2002 and Paper No. 18 filed 6/06/2002] are pending and under examination in the instant office action.

Claims 2, 6-12, 14 and 16-18 were canceled by applicants.

Response to Arguments

Applicants' arguments filed 2/03/2202 and 6/06/2002 have been fully considered but they are not persuasive for the reason below.

Claim Rejections - 35 USC § 112

New matter

Claims 1, 3, 4 and 15 as amended are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Insertion of the limitation "oocyte has undergone at least one cell division" in claims 1 and 15 has no support in the as-filed specification. The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genus which would show possession of the concept of maintaining oocyte till the "oocyte has undergone at least one cell division" wherein the maintaining step indicates activation of oocyte. There is some exemplified disclosure which demonstrates that calcium oscillation is an indication of activation of oocytes,

for example: see Figure 4. The generic applicants' definitions of oocyte activation are also drawn to calcium oscillation as well as to migration of pronuclei within the cell (specification page 5, lines 28-31) rather than cell division(s) as encompassed by the presently claimed method. This disclosure is not sufficient support for the new concept related to indication of oocyte activation as presently claimed. This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of the phrase "oocyte has undergone at least one cell division" is considered to be the insertion of new matter for the above reasons.

Indefinite

Claims 1, 3-5, 13 and 15 as amended are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

All claims are rendered indefinite by repetitions of phrases "said oocyte" because it is uncertain what oocytes are used in each and every step of the methods, what are differences between oocytes at the beginning and at the end of each and every step.

Claims 1, 5 and 15 are indefinite with regard to indication of oocyte activation. It is uncertain what is measured in order to evaluate oocyte activation.

Claims 1 and 15 are rendered indefinite by the phrase "maintaining step indicates that the oocyte is activated" because it is unclear what feature indicates oocyte activation in the maintaining step as intended.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Applicants are hereby notified that the insertion of new matter in the claims or insertion of limitation such as "oocyte has undergone at least one cell division" which encompasses indication (evaluation) of oocyte activation by at least one and more cell division(s) has necessitated the removal of the art rejection over the claims 1 and 15 under 35 U.S.C. 102(b) as being anticipated by Grumetto et al. [U] or over the claims 1, 3, 5 and 15 under 35 U.S.C. 102(b) as being anticipated by Jawerbaum et al. [V]. However, removal of new matter will result in the reinstatement of the art rejection(s).

Claims 1, 3, 4 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,255,109 [A].

Claims are directed to a method of activating oocytes wherein the method comprises a step of contacting an oocyte with a donor of nitric oxide (NO donor) and step of maintaining the oocyte until the oocyte has undergone at least one cell division wherein maintaining step indicates that the oocyte is activated and wherein activation is performed in the absence of sperm. Some claims are further drawn to the use of mammalian oocytes including human oocytes.

US 6,255,109 [A] discloses a method of promoting development of mammalian oocytes or activating oocytes wherein the method comprises step of contacting an oocyte with NO donor or sodium nitroprusside (SNP) and step of maintaining the oocyte until the oocyte has undergone at least one cell division or more than one cell divisions (see table 1, col. 6). The cited patent discloses treatment of mammalian oocytes including bovine and human oocytes (col. 5, line 12; col. 18, line 39). The oocytes were inseminated and, thus, the disclosed method comprises step of contacting oocyte with sperm as required by some of the claims (claim 15). The oocytes were treated with SNP after insemination and, thus, the maintaining step which "indicates" activation is performed in the absence of sperm suspension or in the absence of sperm as required by some of the claims (claim 1). The oocytes treated with SNP are maintained till they have undergone several cell divisions (table 1) and, thus, the maintaining step of the cited method indicates that

the oocytes are activated as required by the presently claimed method. Thus, the cited patent appears to anticipate the claimed invention.

Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Herrero et al. [W].

Claim is directed to a method of inhibiting oocyte activation during fertilization *in vitro* wherein the method comprises a step of contacting an oocyte with sperm and nitric oxide synthase inhibitor.

Herrero et al. [W] disclose a method of inhibiting oocyte activation during fertilization *in vitro* wherein the method comprises step of contacting mouse oocyte with sperm and various nitric oxide synthase inhibitors. The reference teaches the decrease of fertilization after the use of nitric oxide synthase inhibitors *in vitro* (table 1) and, thus, the cited reference teaches inhibition of oocyte activation during fertilization *in vitro* to the extend of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 13 and 15 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,255,109 [A] and Herrero et al. [W].

Claims are directed to a method of modulating activation of oocytes comprising steps of contacting an oocyte with a modulator of nitric oxide level such as a donor of NO or an inhibitor of nitric oxide synthase (NOS inhibitor) in the *in vitro* system and maintaining oocytes till at least one cell division. Some claims are further drawn to oocyte activation/modulation in the absence of sperm or prior to sperm addition. Some claims are further drawn to the use of oocytes including mammalian or human oocytes.

US 6,255,109 [A] and Herrero et al. [W] are relied upon as explained above for the disclosure of methods of modulating activation of oocytes with NO donors {US 6,255,109 [A]) and/or inhibitors of nitric oxide synthase {Herrero et al. [W]} and maintaining oocytes till cell divisions after treatment with NO level modulators. The cited references teach the use of various mammalian oocytes including mouse {Herrero et al. [W]}, bovine and humans {US 6,255,109 [A]}.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the present invention as claimed with a reasonable expectation of success in activating oocytes intended for cell development and growth by treating oocytes with NO level modulators because it is known to use NO level modulators in the systems intended for oocyte development and growth. Thus, one of skill in the art would have been motivated to use compounds which are NO level modulators for the benefit of oocyte

development and growth. The method of the present invention is related to activation of oocytes derived from a wide variety of animal species including invertebrate species, mammalians and etc. (specification page 9, line 11) as it is demonstrated by the cited prior art [U, V, IDS-AB]. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Claims 1, 3-5, 13 and 15 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over Grumetto et al. [U] taken with Jawerbaum et al. [V] and US 6,077, 710 [IDS-AB] as explained in the prior office action and for the reasons below.

Claims are directed to a method of modulating activation of oocytes comprising step of contacting an oocyte with a modulator of nitric oxide level such as a donor of NO or an inhibitor of nitric oxide synthase (NOS inhibitor) in an *in vitro* system. Some claims are further drawn to oocyte activation/modulation in the absence of sperm or prior to sperm addition. Some claims are further drawn to the use of oocytes including mammalian or human oocytes.

The references by Grumetto et al. [U] and Jawerbaum et al. [V] are relied upon for the disclosure of methods of modulating activation of oocytes by contacting oocytes with modulators of NO levels such as NO donors or NOS inhibitors prior to sperm addition, insemination and, thus, prior to cell division(s).

For example, Jawerbaum et al. [V] disclose a method of modulating activation of mammalian oocytes comprising step of contacting *in vitro* cultured and maturated rat oocytes (page 392, par. 3, line 2) with modulators of nitric oxide levels such as NO donors (sodium nitroprusside, for example) and/or inhibitors of nitric oxide synthase (L-NAME, for example) in the absence of sperm. In particular, the cited reference teaches modulation of synthesis and accumulation of hormones which are involved in oocyte maturation, ovulation and fertilization processes.

The reference by Grumetto et al. [U] disclose a method of modulating activation of oocytes of the ascidian *Ciona intestnalis* wherein the method comprises a step of contacting an oocyte with a modulator of nitric oxide level or NO donor such as sodium nitroprusside in the *in vitro* system (abstract). The reference also discloses modulation of NO level or oocyte activation during fertilization (Fig. 4) in the presence of sperm. Further, the cited reference by Grumetto et al. [U] teaches an induction of fertilization current or Ca^{2+} currents by modulation of NO level (abstract). But the cited reference by Grumetto et al. [U] is lacking the teaching related to activation of mammalian oocytes.

However, the cited patent US 6,077, 710 [IDS-AB] teaches that activation of mammalian oocytes is a function of calcium (Ca^{2+}) (col. 2, line 42) and that parthenogenic activation of oocytes prior to nuclear transfer and related to repetitive transient elevations in intracellular Ca^{2+} in mammalian oocytes (col. 2, lines 47-50 and col. 3, lines 3-310) including various mammalian oocytes such as rabbit, bovine and/or mouse oocytes.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the present invention as claimed with a reasonable expectation of success in activating oocytes or inducing Ca^{2+} fluctuations in oocytes by treating oocytes with NO level modulators because the prior art teaches that activation of oocytes and/or fertilization channels are modulated by NO levels {Grumetto et al. [U]} and that activation of oocytes is related to Ca^{2+} fluctuations in oocytes including mammalian oocytes belonging to various mammalian species {US 6,077, 710 [IDS-AB]}. One of skill in the art would have been motivated to use compounds which are NO level modulators for the benefit of modulating Ca^{2+} fluctuations in the oocytes intended for future fertilization or nuclear transfers. The method of the present invention is related to activation of oocytes derived from a wide variety of animal species including invertebrate species, mammalians and etc. (specification page 9, line 11) as it is demonstrated by the cited prior art [U, V, IDS-AB]. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

With regard to the claims rejection under 35 U.S.C. § 103 applicants' main argument is directed to the idea that the references by Grumetto et al. [U] and by Jawerbaum et al. [V] fail to teach cell division(s) after activation of oocytes with NO level modulators (see response page 6, par.. However, according to the applicants' definitions the oocyte activation is an increase (or

fluctuation) of intracellular Ca^{2+} levels (see instant specification page 5, line 30-31 for definitions and Figures 4-6 for particular results) rather than cell division(s). No cell division is demonstrated by applicants as the result of oocyte treatment with modulators of NO level. The cited reference by Grumetto et al. [U] clearly teaches an increase of intracellular Ca^{2+} as the result of addition of NO donor to oocytes (see page 724, col. 2, par. 4, line 2-4). Therefore, the cited references are considered to be within the same field of endeavor and seek to solve the same problems as the instant application and claims, and one of skill in the art is free to select components available in the prior art. In re Winslow, 151 USPQ 48 (CCPA, 1966).

Applicants also argued that the cited references combined do not provide a clear connection between modulating NO levels and mammalian oocyte activation and/or fluctuations of Ca^{2+} levels (response page 7, par. 2). This is not found particularly convincing since the references by Grumetto et al. [U] teaches an induction of fertilization current or fluctuations of Ca^{2+} levels by modulation of NO level (see abstract, for example). And the cited US 6,077, 710 [IDS-AB] teaches that activation of oocytes or reentry into mitotic cycle of mammalian oocytes is directly related to cellular activity which is a function of Ca^{2+} levels (col. 2, lines 32-42). 42) and that activation of oocytes of various mammalian species is characterized by fluctuations of intracellular Ca^{2+} levels (col. 3, lines 3-30).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova,

Art Unit 1651

September 5, 2002.

IRENE MARX
PRIMARY EXAMINER